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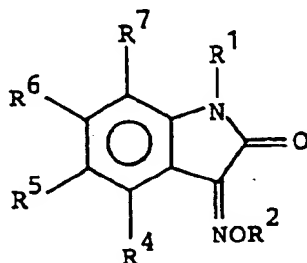
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(54) **Isatine derivatives, their preparation and use.**

(57) A method of treatment with compounds having the formula



wherein

R<sup>1</sup> is hydrogen, C<sub>1-6</sub>-alkyl which may be branched, C<sub>3-7</sub>-cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C<sub>1-6</sub>-alkoxy, CH<sub>2</sub>CO<sub>2</sub>R' wherein R' is hydrogen or C<sub>1-6</sub>-alkyl which may be branched, CH<sub>2</sub>CN, CH<sub>2</sub>CONR<sup>IV</sup>R<sup>V</sup> wherein R<sup>IV</sup> and R<sup>V</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, or

CH<sub>2</sub>C(=NOH)NH<sub>2</sub>;

R<sup>2</sup> is hydrogen, benzyl, C<sub>1-6</sub>-alkyl which may be branched, or C<sub>3-7</sub>-cycloalkyl;

R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl which may be branched, phenyl, halogen, C<sub>1-6</sub>-alkoxy, NO<sub>2</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CF<sub>3</sub>; or R<sup>6</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partially saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, and R<sup>4</sup> and R<sup>5</sup> have the meanings set forth above, are disclosed, as well as pharmaceutical compositions thereof. Certain of the compounds are novel.

The compounds and pharmaceutical compositions containing the compounds are useful in the treatment of central nervous system disorders and especially conditions sensitive to excitatory amino acids.

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## ISATINE DERIVATIVES, THEIR PREPARATION AND USE

The present invention relates to a method of treatment with compounds having excitatory amino acid antagonizing properties, pharmaceutical compositions comprising such compounds, and to novel compounds having excitatory amino acid antagonizing properties and to the preparation of such compounds.

It is an object of the present invention to provide a method of treating diseases in mammals, including a human, by antagonizing an excitatory amino acid in such mammal.

A second object of the present invention is to provide novel pharmaceutical compositions useful for the treatment of diseases in mammals, including a human, acting by antagonizing an excitatory amino acid in such mammal.

A third object of the present invention is to provide novel compounds useful for the treatment of diseases in mammals, including a human, acting by antagonizing an excitatory amino acid in such mammal.

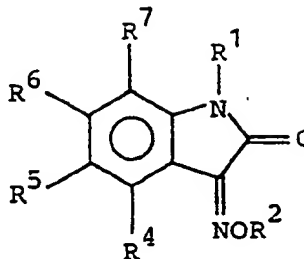
#### Background of the Invention

It is well known from  
Wiss. Z. Ernst-Moritz-Arndt-Univ. Greifswald, Math.-nat.wiss.  
Reihe 35, 39-44 (1986) 4,  
Pharmazie 39, H.10, 713 (1984),  
Pharmazie 37, H.12, 858-861 (1982),  
Neuroscience Letters 107, 327-330 (1989),  
PCT patent application International Publication Number WO 89/03818, and  
Khim.-Farm.zh. 23(11), 1349-1352 (1989),  
that certain of the chemical entities comprised within the scope of method of treatment according to the present invention are known to possess biological activity.

#### Summary of the Invention

The invention then, *inter alia*, comprises the following, alone or in combination:

A method of antagonizing the biological effects of an excitatory amino acid of a subject in need of such antagonization comprising the step of administering to said subject an effective excitatory amino acid antagonizing amount of an indole-2,3-dione-3-oxime compound having the formula



wherein

R¹ is hydrogen, C<sub>1-6</sub>-alkyl which may be branched, C<sub>3-7</sub>-cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C<sub>1-6</sub>-alkoxy, CH<sub>2</sub>CO<sub>2</sub>R' wherein R' is hydrogen or C<sub>1-6</sub>-alkyl which may be branched, CH<sub>2</sub>CN, CH<sub>2</sub>CONR<sup>IV</sup>R<sup>V</sup> wherein R<sup>IV</sup> and R<sup>V</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, or CH<sub>2</sub>C(=NOH)NH<sub>2</sub>;

R² is hydrogen, benzyl, C<sub>1-6</sub>-alkyl which may be branched, or C<sub>3-7</sub>-cycloalkyl;

R⁴, R⁵, R⁶, R⁷ independently are hydrogen, C<sub>1-6</sub>-alkyl which may be branched, phenyl, halogen, C<sub>1-6</sub>-alkoxy, NO<sub>2</sub>, CN, CF<sub>3</sub>, or SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl; or R⁵ and R⁷ together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, and R⁴ and R⁵ have the meanings set forth above,

a method as above wherein at least one of R⁴, R⁵, R⁶ or R⁷ is an electron withdrawing substituent such as NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''', or halogen and R¹, R², R⁴, R⁵, R⁶, R⁷, R'', and R''' otherwise have the meanings set forth,

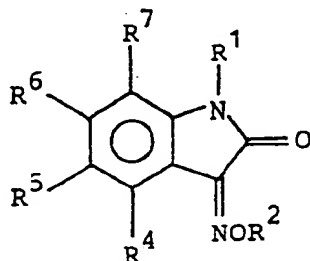
a method as first above wherein R⁵ is NO<sub>2</sub>, F, CF<sub>3</sub>, or CN,

moreover a method of antagonizing the biological effects of an excitatory amino acid as first above, wherein the compound is administered in the form of a pharmaceutical composition thereof, in which it is present together with a pharmaceutically acceptable carrier or diluent,

and a method of antagonizing the biological effects of an excitatory amino acid as second above, wherein the compound is administered in the form of a pharmaceutical composition thereof, in which it is present together with a pharmaceutically acceptable carrier or diluent,

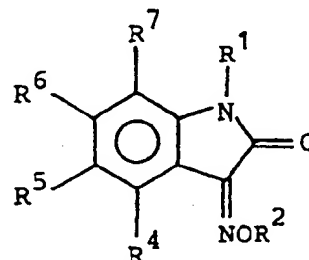
further a pharmaceutical composition for use in antagonizing the biological effects of an excitatory amino acid of a subject in need of such an-

tagonization comprising an effective excitatory amino acid antagonizing amount of a compound having the formula

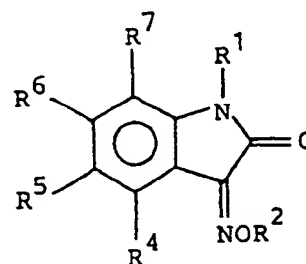


R<sup>1</sup> is hydrogen;  
 R<sup>2</sup> is hydrogen, benzyl, C<sub>1-6</sub>-alkyl which may be branched, or C<sub>3-7</sub>-cycloalkyl;  
 R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl which may be branched, phenyl, halogen, C<sub>1-6</sub>-alkoxy, NO<sub>2</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CF<sub>3</sub>, or R<sup>6</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, and R<sup>4</sup> and R<sup>5</sup> have the meanings set forth above, at least one of R<sup>4</sup>, R<sup>5</sup> and R<sup>7</sup> are other than hydrogen when R<sup>5</sup> is not other than H, Cl or Br;  
 or R<sup>1</sup> is C<sub>1-6</sub>-alkyl which may be branched, C<sub>3-7</sub>-cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C<sub>1-6</sub>-alkoxy, CH<sub>2</sub>CO<sub>2</sub>R' wherein R' is hydrogen or C<sub>1-6</sub>-alkyl which may be branched, CH<sub>2</sub>CN, CH<sub>2</sub>CONR<sup>IV</sup>R<sup>V</sup> wherein R<sup>IV</sup> and R<sup>V</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, CH<sub>2</sub>C(=NOH)NH<sub>2</sub>;  
 R<sub>2</sub> is hydrogen, benzyl, C<sub>1-6</sub>-alkyl which may be branched, or C<sub>3-7</sub>-cycloalkyl;  
 R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl which may be branched, phenyl, halogen, C<sub>1-6</sub>-alkoxy, NO<sub>2</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CF<sub>3</sub>, or R<sup>6</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, and R<sup>4</sup> and R<sup>5</sup> have the meanings set forth above, at least one of R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are other than hydrogen when R<sup>1</sup> is not other than methyl, at least one of R<sup>4</sup> and R<sup>5</sup> are other than hydrogen when R<sup>1</sup> is not other than phenyl which may be substituted, and at least one of R<sup>4</sup> and R<sup>5</sup> are other than hydrogen when R<sup>6</sup> and R<sup>7</sup> together form an additional benzene ring,  
 and method of antagonizing the biological effects

of an excitatory amino acid of a subject in need thereof comprising the step of administering to said subject a pharmaceutical composition as above, further a compound having the formula



wherein R<sup>1</sup> is C<sub>1-6</sub>-alkyl which may be branched, C<sub>3-7</sub>-cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C<sub>1-6</sub>-alkoxy, CH<sub>2</sub>CO<sub>2</sub>R' wherein R' is hydrogen or C<sub>1-6</sub>-alkyl which may be branched, CH<sub>2</sub>CN, CH<sub>2</sub>CONR<sup>IV</sup>R<sup>V</sup> wherein R<sup>IV</sup> and R<sup>V</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, or CH<sub>2</sub>C(=NOH)NH<sub>2</sub>; R<sup>2</sup> is hydrogen, benzyl, C<sub>1-6</sub>-alkyl which may be branched, or C<sub>3-7</sub>-cycloalkyl;  
 R<sup>5</sup> is NO<sub>2</sub>, F, CF<sub>3</sub>, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CN; and  
 R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl which may be branched, phenyl, halogen, C<sub>1-6</sub>-alkoxy, NO<sub>2</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CF<sub>3</sub>, or R<sup>6</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, R<sup>4</sup> has the meaning set forth above,  
 and a compound having the formula

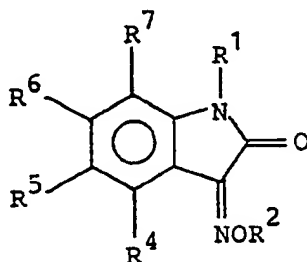


wherein R<sub>1</sub> is C<sub>1-6</sub>-alkyl which may be branched, C<sub>3-7</sub>-cycloalkyl, benzyl, acyl, hydroxy, C<sub>1-6</sub>-alkoxy, CH<sub>2</sub>CO<sub>2</sub>R' wherein R' is hydrogen or C<sub>1-6</sub>-alkyl which may be branched, CH<sub>2</sub>CN, CH<sub>2</sub>CONR<sup>IV</sup>R<sup>V</sup> wherein R<sup>IV</sup> and R<sup>V</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, or CH<sub>2</sub>C(=NOH)NH<sub>2</sub>; R<sup>2</sup> is hydrogen, benzyl, C<sub>1-6</sub>-alkyl which may be

branched, or C<sub>3-7</sub>-cycloalkyl;

R<sup>5</sup> is NO<sub>2</sub>, F, CF<sub>3</sub>, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CN; and

R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl which may be branched, phenyl, halogen, C<sub>1-5</sub>-alkoxy, NO<sub>2</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CF<sub>3</sub>, or R<sup>6</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, and R<sup>4</sup> has the meaning set forth above, and a compound having the formula



wherein

R<sup>1</sup> is hydrogen,

R<sup>2</sup> is hydrogen, benzyl, C<sub>1-6</sub>-alkyl which may be branched, or C<sub>3-7</sub>-cycloalkyl;

R<sup>5</sup> is NO<sub>2</sub>, F, CF<sub>3</sub>, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CN; and

R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl which may be branched, phenyl, halogen, C<sub>1-5</sub>-alkoxy, NO<sub>2</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CF<sub>3</sub>, or R<sup>6</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, and R<sup>4</sup> has the meaning set forth above; and that R<sup>5</sup> is different from NO<sub>2</sub> and F when R<sup>1</sup>, R<sup>4</sup>, R<sup>6</sup> and R<sup>7</sup> are not other than hydrogen and R<sup>2</sup> is not other than hydrogen or benzyl; and that R<sup>5</sup> is different from NO<sub>2</sub> when R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup> and R<sup>6</sup> are not other than hydrogen and R<sup>7</sup> is not other than NO<sub>2</sub>.

further a compound as above wherein R<sup>4</sup> and R<sup>5</sup> independently are hydrogen, F, NO<sub>2</sub>, CN, CF<sub>3</sub>, or SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, and wherein R<sup>6</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently

are hydrogen or C<sub>1-6</sub>-alkyl,

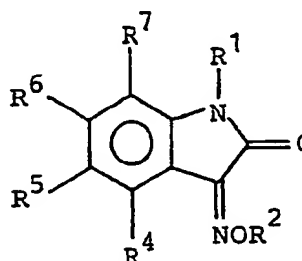
and a compound as above wherein the additional ring formed by R<sup>6</sup> and R<sup>7</sup> is substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN or SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl,

and a compound as above, which is 5-nitro-1H-benz[g]indole-2,3-dione-3-oxime,

and a compound as above, which is 5,7-dinitro-1-methyl-1H-indole-2,3-dione-3-(O-methyloxime),

and a compound as above, which is 5-nitro-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione-3-oxime,

moreover a method of treating a central nervous system disorder in a subject in need of such treatment, comprising the step of administering to said subject an effective amount of a compound having the formula

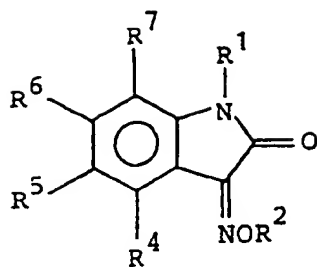


wherein R<sup>1</sup> is hydrogen, C<sub>1-6</sub>-alkyl which may be branched, C<sub>3-7</sub>-cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C<sub>1-5</sub>-alkoxy, CH<sub>2</sub>CO<sub>2</sub>R' wherein R' is hydrogen or C<sub>1-5</sub>-alkyl which may be branched, CH<sub>2</sub>CN, CH<sub>2</sub>CONR<sup>IV</sup>R<sup>V</sup> wherein R<sup>IV</sup> and R<sup>V</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, or CH<sub>2</sub>C(=NOH)NH<sub>2</sub>; R<sup>2</sup> is hydrogen, benzyl, C<sub>1-6</sub>-alkyl which may be branched, or C<sub>3-7</sub>-cycloalkyl;

R<sup>5</sup> is NO<sub>2</sub>, F, CF<sub>3</sub>, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CN; and

R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl which may be branched, phenyl, halogen, C<sub>1-5</sub>-alkoxy, NO<sub>2</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CF<sub>3</sub>, or R<sup>6</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, and R<sup>4</sup> has the meaning set forth above; and that R<sup>5</sup> is different from NO<sub>2</sub> and F when R<sup>1</sup>, R<sup>4</sup>, R<sup>6</sup> and R<sup>7</sup> are not other than hydrogen and R<sup>2</sup> is not other than hydrogen or benzyl; and that R<sup>5</sup> is different from NO<sub>2</sub> when R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup> and R<sup>6</sup> are not other than hydrogen and R<sup>7</sup> is not other than NO<sub>2</sub>,

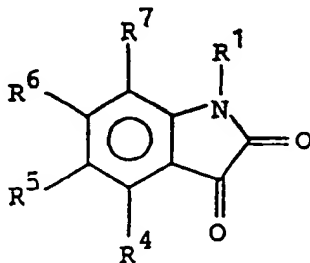
further a method of preparing a compound having the formula



wherein R<sup>1</sup> is hydrogen, C<sub>1-6</sub>-alkyl which may be branched, C<sub>3-7</sub>-cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C<sub>1-6</sub>-alkoxy, CH<sub>2</sub>CO<sub>2</sub>R' wherein R' is hydrogen or C<sub>1-6</sub>-alkyl which may be branched, CH<sub>2</sub>CN, CH<sub>2</sub>CONR<sup>IV</sup>R<sup>V</sup> wherein R<sup>IV</sup> and R<sup>V</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, or CH<sub>2</sub>C(=NOH)NH<sub>2</sub>; R<sup>2</sup> is hydrogen, benzyl, C<sub>1-6</sub>-alkyl which may be branched, or C<sub>3-7</sub>-cycloalkyl;

R<sup>5</sup> is NO<sub>2</sub>, F, CF<sub>3</sub>, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CN; and

R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl which may be branched, phenyl, halogen, C<sub>1-6</sub>-alkoxy, NO<sub>2</sub>, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, CN, or CF<sub>3</sub>, or R<sup>6</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, and R<sup>4</sup> has the meaning set forth above; and that R<sup>5</sup> is different from NO<sub>2</sub> and F when R<sup>1</sup>, R<sup>4</sup>, R<sup>6</sup> and R<sup>7</sup> are not other than hydrogen and R<sup>2</sup> is not other than hydrogen or benzyl; and that R<sup>5</sup> is different from NO<sub>2</sub> when R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup> and R<sup>6</sup> are not other than hydrogen and R<sup>7</sup> is not other than NO<sub>2</sub>, comprising the step of reacting a compound of the formula

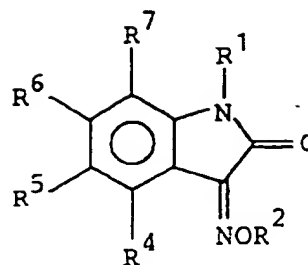


wherein R<sup>1</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> have the meanings set forth above, with a compound having the formula NH<sub>2</sub>OR<sup>2</sup>, wherein R<sup>2</sup> has the meaning set forth above,

and moreover the use of a compound having the formula

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wherein

R<sup>1</sup> is hydrogen, C<sub>1-6</sub>-alkyl which may be branched, C<sub>3-7</sub>-cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C<sub>1-6</sub>-alkoxy, CH<sub>2</sub>CO<sub>2</sub>R' wherein R' is hydrogen or C<sub>1-6</sub>-alkyl which may be branched, CH<sub>2</sub>CN, CH<sub>2</sub>CONR<sup>IV</sup>R<sup>V</sup> wherein R<sup>IV</sup> and R<sup>V</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, or CH<sub>2</sub>C(=NOH)NH<sub>2</sub>;

R<sup>2</sup> is hydrogen, benzyl, C<sub>1-6</sub>-alkyl which may be branched, or C<sub>3-7</sub>-cycloalkyl;

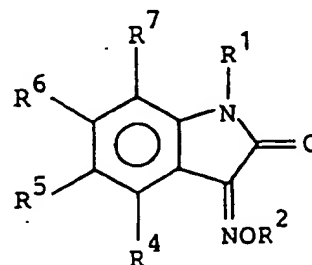
R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl which may be branched, phenyl, halogen, C<sub>1-6</sub>-alkoxy, NO<sub>2</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CF<sub>3</sub>; or R<sup>6</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, and R<sup>4</sup> and R<sup>5</sup> have the meanings set forth above, for the preparation of a medicament useful in the treatment of conditions sensitive to an excitatory amino acid,

and the use as above wherein at least one of R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup> is an electron withdrawing substituent such as NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''', or halogen and R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R'' and R''' otherwise have the meanings set forth above.

and further a method of preparing a pharmaceutical preparation containing as active ingredient an effective amount of a compound having the formula

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wherein

R<sup>1</sup> is hydrogen, C<sub>1-6</sub>-alkyl which may be

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branched, C<sub>3-7</sub>-cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C<sub>1-6</sub>-alkoxy, CH<sub>2</sub>CO<sub>2</sub>R' wherein R' is hydrogen or C<sub>1-6</sub>-alkyl which may be branched, CH<sub>2</sub>CN, CH<sub>2</sub>CONR<sup>IV</sup>R<sup>V</sup> wherein R<sup>IV</sup> and R<sup>V</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, or CH<sub>2</sub>C(=NOH)NH<sub>2</sub>;

R<sup>2</sup> is hydrogen, benzyl, C<sub>1-6</sub>-alkyl which may be branched, or C<sub>3-7</sub>-cycloalkyl;

R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl which may be branched, phenyl, halogen, C<sub>1-6</sub>-alkoxy, NO<sub>2</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CF<sub>3</sub>; or R<sup>6</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, and R<sup>4</sup> and R<sup>5</sup> have the meanings set forth above.

Preferred compounds to be employed according to the invention and preferred compounds according to the invention per se are for example:

5,7-dinitro-1-methyl-1H-indole-2,3-dione-3-(O-methyloxime)  
5-bromo-7-nitro-1H-indole-2,3-dione-3-oxime,  
5,7-dinitro-1-methyl-1H-indole-2,3-dione-3-oxime,  
5-nitro-1H-benz[g]indole-2,3-dione-3-oxime,  
5-nitro-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione-3-oxime.

#### Biological Activity

The compounds of the invention exhibit valuable biological properties because of their strong excitatory amino acid (EAA) (glycine, glutamate, quisqualate, ATPA, AMPA, kainate, NMDA) antagonizing properties.

For example compounds of the invention exhibit strong pharmacological *in vivo* ATPA and quisqualate antagonizing effects demonstrating their utility as novel orally-bioavailable excitatory amino acid antagonists, which makes them useful in the treatment of for example excitatory amino acid dependent psychosis, excitatory amino dependent anoxia, excitatory amino acid dependent ischemia, excitatory amino acid dependent convulsions, and excitatory amino acid dependent migraine.

Compounds of the invention will inhibit ATPA-induced rigidity and quisqualate or NMDA-induced convulsions with an ED<sub>50</sub> in the range of 0.1-10.0 mg/kg. Examples of such compounds are 5,7-dinitro-1-methyl-1H-indole-2,3-dione-3-(O-methyloxime) and 5,7-dinitro-1-(ethoxy carbonyl methyl)-1H-indole-2,3-dione-3-(O-methyloxime).

Compounds of the invention show potent *in vitro* affinity for the glutamate subreceptors kainate, quisqualate and glycine receptors. These properties make the compounds useful in the treatment of

human malfunctions related to the excitatory amino acids (EAA).

For example some compounds of the invention exhibit binding at the <sup>3</sup>H-kainate, <sup>3</sup>H-AMPA and/or <sup>3</sup>H-glycine binding sites with IC<sub>50</sub> in the range of 10-100 μM. Examples of such compounds are for example

5-bromo-7-nitro-1H-indole-2,3-dione-3-oxime,  
5-nitro-1H-indole-2,3-dione-3-oxime,  
5,7-dinitro-1H-indole-2,3-dione-3-oxime,  
5,7-dinitro-1-methyl-1H-indole-2,3-dione-3-oxime,  
1H-benz[g]indole-2,3-dione-3-oxime,  
5-nitro-1H-benz[g]indole-2,3-dione-3-oxime, and  
5-nitro-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione-3-oxime.

Also the compounds of the invention as a secondary result of their EAA-antagonizing properties have been found to antagonize cocaine-induced hypermotility. For example the most potent compounds of the invention have been found to have an ED<sub>50</sub> in the range of 0.5-1.0 mg/kg in this test when administered orally. An example of such a compound is 5,7-dinitro-1-methyl-1H-indole-2,3-dione-3-(O-methyloxime).

Furthermore it has been found that some of the compounds of the invention are metabolites of other compounds of the invention and that the metabolites exhibit biological activity in the same range or are even more potent than the precursor compounds of the invention. Accordingly both such parent or precursor compounds and such metabolites fall within the scope of the invention. Some of the compounds named in the foregoing will be recognized as metabolites of precursor compounds named in the foregoing, and vice versa.

Such metabolites are for example:

N-dealkylated derivatives, 1-N-hydroxyalkyl derivatives, 1-N-hydroxy derivatives, 1-N-oxide derivatives, O-dealkylated derivatives, pyrrolo ring opened hydrolyzed derivatives, pyrrolo ring opened hydrolyzed and decarboxylated derivatives as well as combinations of such metabolisation reactions.

#### Biological testing

The above mentioned tests are performed as described in more detail below and are based upon the principles also described hereinafter.

#### ATPA-induced rigidity

The selective quisqualate receptor agonist ATPA induces rigidity in female NMRI mice at doses between 3 and 15 mg/kg and clonic-tonic seizures and death, probably due to respiratory arrest, at doses between 15 and 40 mg/kg after intravenous (i.v.) administration.

### Method

ATPA ((RS)- $\alpha$ -amino-3-hydroxy-5-tert-butyl-4-isoxazolepropionic acid) was dissolved in distilled water and test compound was dissolved in a polyoxyl 40 hydrogenated castor oil (5% Cremophor RHTM 40 (BASF)).

Test compound was administered either i.v. 5, 30 or 120 min before or p.o. 30 min before an i.v. administration of 15 mg/kg of ATPA to 8 female NMRI mice per dose and the number of mice experiencing rigidity 5 min later was noted. An ED<sub>50</sub> value was calculated from at least three doses of test compound as the dose inhibiting 50% of the mice from having rigidity.

### Quisqualate-induced clonic seizures

Quisqualate given icv (intracerebroventricular) to DBA/2 mice induces clonic seizures which can be inhibited by both NMDA and non-NMDA receptor antagonists after i.v. administration.

### Method

Test compound was given i.v. 5 min before a 20  $\mu$ g icv administration of quisqualate to 10 male DBA/2 mice (weighing 10-12 g) per dose. The number of mice experiencing clonic seizures within the next 2 min was noted. An ED<sub>50</sub> value was calculated as the dose inhibiting 50% of the mice from having clonic seizures.

### NMDA-induced clonic seizures

NMDA given icv to NMRI mice induces clonic seizures which can be inhibited by NMDA receptor antagonists.

### Method

Test compound was given i.v. 5 min before a 0.5  $\mu$ g icv administration of NMDA to 10 male NMRI mice per dose. The number of mice experiencing clonic seizures within the next 2 min was noted. An ED<sub>50</sub> value was calculated as the dose inhibiting 50% of the mice from having clonic seizures.

### Cocaine-induced hypermotility

Quisqualate and kainate administered locally induce an increase in dopamine release in nucleus accumbens and nucleus caudatus accompanied by stereotype behaviour such as hyper-locomotion, rearing, sniffing and grooming. These effects can be inhibited by selective quisqualate antagonists administered locally by the micro-dialysis method.

Also the dopamine uptake inhibitor cocaine administered s.c. induce hypermotility which can be inhibited by an administration of the glutamate antagonist GDEE into nucleus accumbens.

For these reasons (and others) it has been concluded that non-NMDA receptors regulate the release of dopamine in nucleus accumbens and that non-NMDA receptor antagonists can alleviate the symptoms of psychosis.

### Method

Test compound was administered orally at doses of 0.1, 1, 10 and 30 mg/kg 30 min before the administration of 25 mg/kg cocaine i.p. to female NMRI mice and the locomotor activity of 2 mice per box was measured for the next 2 hours by use of 8 infrared photobeams per box. The mice had been adapted to the box for at least 16 hours to avoid exploratory motility (neophobia).

The quisqualate binding assay was performed as described by T. Honoré et al., Neuroscience Letters 54, 27-32 (1985).

The kainate binding assay was performed as described by T. Honoré et al., Neuroscience Letters 65, 47-52 (1986).

The glycine binding assay was performed as described by W. Frost White et al., Journal of Neurochemistry 53(2), 503-512 (1989).

### Pharmaceutical Compositions

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing ten (10) milligrams of active ingredients or, more broadly, 0.1 to one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

Solid forms of pharmaceutical compositions for p.o. administration and injectable solutions are preferred.

### Method of Treating

The compounds of this invention are extremely useful in the treatment of central nervous system disorders related to their biological activity. The compounds of this invention may accordingly be administered to a subject, including a human, in need of treatment, alleviation, or elimination of an indication associated with the biological activity of the compounds. This includes especially excitatory amino acid dependent psychosis, excitatory amino acid dependent anoxia, excitatory amino acid dependent ischemia, excitatory amino acid dependent convulsions and excitatory amino acid dependent migraine. Suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

### Chemical Examples

Some compounds of the invention are old, and others are novel chemical entities. In any-way the compounds of the invention may be prepared according to chemical methods which are well known.

#### Example 1

##### a) 1-phenyl-1H-indole-2,3-dione.

To a stirred solution of diphenylamine (3.2 g, 20 mmol) and 4-dimethylaminopyridine (10 mg) in chloroform (50 ml) was dropwise added oxalylchloride (3 ml). The resulting mixture was refluxed for 5 hours, whereafter it was cooled to room temperature and evaporated in vacuo.

The residue (oil) was redissolved in methylene chloride (50 ml) and dry  $\text{AlCl}_3$  (3 g) was added. Stirring at room temperature was continued for 30 hours, whereafter ethanol (10 ml) followed by water (100 ml) were added. The organic phase was washed with saturated  $\text{Na}_2\text{CO}_3$ , dried over  $\text{Na}_2\text{SO}_4$  and evaporated. The crystalline residue was stirred in ether (40 ml) and the product was filtered off. Yield: 2.65 g orange crystals, M.p. 139-141 °C, litt. 138 °C.

b) The following 1H-indole-2,3-diones were prepared according to known literature procedures. 4,6-ditrifluoromethyl-1H-indole-2,3-dione <sup>1)</sup>, M.p.

162-165 °C.

1H-benz[g]indole-2,3-dione <sup>2)</sup>, M.p. 242-245 °C.

7-trifluoromethyl-1H-indole-2,3-dione <sup>1)</sup>, M.p. 181-183 °C.

1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione, M.p. 224-226 °C.

6-methoxy-1H-indole-2,3-dione, M.p. >310 °C.

7-trifluoromethyl-1H-indole-2,3-dione, M.p. 180-184 °C.

c) 1-methyl-5-nitro-7-trifluoromethyl-1H-indole-2,3-dione.

To a stirred 10 °C warm solution of  $\text{KNO}_3$  - (0.5 g) in 10 ml of conc.  $\text{H}_2\text{SO}_4$  was dropwise added a solution of 1-methyl-7-trifluoromethyl-1H-indole-2,3-dione in 10 ml of conc.  $\text{H}_2\text{SO}_4$ . The addition was completed after 10 min, whereafter stirring was continued for 15 min at room temperature. The reaction mixture was poured on ice whereby the title compound precipitated as yellow crystals. The crystals were collected by filtration and washed with water. M.p. 168-169 °C.

In a similar manner to c), the following nitro compounds were prepared:

5-nitro-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione, M.p. 232-236 °C.

5-nitro-1-methyl-1H-benz[g]indole-2,3-dione, M.p. 255-258 °C.

d) 5,7-dinitro-1-methyl-1H-indole-2,3-dione.

To a stirred solution of 5,7-dinitro-1H-indole-2,3-dione (1.2 g) in dry dimethylformamide (20 ml) was added sodium hydride (0.24 g 55% in mineral oil). After the hydrogen evolution had ceased methyl iodide (0.37 ml) was added. Stirring at room temperature was continued for 2 hours, whereafter the crude product was precipitated as an oil by addition of water (100 ml) to the reaction mixture. The oil crystallized upon treatment with ether/pentane. M.p. 154-157 °C.

In a similar manner to d), the following 1-alkyl- or 1-benzyl-1H-indole-2,3-diones were prepared.

5,7-dinitro-1-ethyl-1H-indole-2,3-dione, M.p. 135-140 °C.

5-bromo-1-methyl-1H-indole-2,3-dione, M.p. 157-160 °C.

1H-1-methyl-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione, M.p. 157-160 °C.

5,7-dibromo-1-methyl-1H-indole-2,3-dione, M.p. 170-173 °C.

5,6-dichloro-1-methyl-1H-indole-2,3-dione, M.p.

<sup>1)</sup>Organic Synthesis Col Vol. I p. 327.

<sup>2)</sup>Martinet, J.: Compt. Rend. 166, 851, 1918.



180-184 °C.  
 4,5-dichloro-1-methyl-1H-indole-2,3-dione, M.p. 237-239 °C.  
 1-methyl-5-nitro-1H-indole-2,3-dione, M.p. 196-199 °C.  
 1-benzyl-5,7-dinitro-1H-indole-2,3-dione, M.p. 127-131 °C.  
 4,6-ditrifluoromethyl-1-methyl-1H-indole, M.p. 93-94 °C.  
 1-methyl-7-trifluoromethyl-1H-indole-2,3-dione, M.p. 120-122 °C.  
 6-methoxy-1-methyl-1H-indole-2,3-dione, M.p. 175-178 °C.  
 5,7-dinitro-1-(ethoxycarbonylmethyl)-1H-indole-2,3-dione, (oil).  
 1-methyl-1H-benz[g]indole-2,3-dione, M.p. 122-126 °C.  
 1-(ethoxycarbonylmethyl)-1H-indole-2,3-dione, M.p. 115-119 °C.  
 5,7-dibromo-1-(ethoxycarbonylmethyl)-1H-indole-2,3-dione, M.p. 97-102 °C.  
 1-methyl-1H-6,7,8,9-tetrahydrobenz[g]indole-2,3-dione, M.p. 160-165 °C.

#### Example 2

5,7-dinitro-1-methyl-1H-indole-2,3-dione-3-(O-methyloxime).

5,7-dinitro-1-methyl-1H-indole-2,3-dione (0.4 g), O-methyl-hydroxylamine, hydrochloride (0.16 g) and sodium carbonate (0.2 g) was stirred at room temperature in ethanol (5 ml) for one hour, whereafter acetic acid (0.5 ml) followed by water (50 ml) were added. The mixture was cooled on ice and the crystalline product was obtained by filtration, M.p. 145-151 °C.

The following O-alkyloximes were prepared in a similar manner starting from the appropriate indole-2,3-diones.

5,7-dinitro-1H-indole-2,3-dione-3-(O-methyloxime), M.p. 236-239 °C.  
 5,7-dinitro-1-ethyl-1H-indole-2,3-dione-3-(O-methyloxime), M.p. 156-159 °C.  
 5-nitro-3-(O-methyloxime)-1H-indole-2,3-dione, M.p. 293-295 °C.  
 1-phenyl-1H-indole-2,3-dione-3-(O-methyloxime), M.p. 151-153 °C.  
 1H-indole-2,3-dione-3-(O-methyloxime), M.p. 168-171 °C.  
 5,7-dibromo-1-methyl-1H-indole-2,3-dione-3-(O-methyloxime), M.p. 170-172 °C.  
 5,7-dibromo-1H-indole-2,3-dione-3-(O-methyloxime), M.p. 279 °C (decomp.).  
 1-methyl-5-nitro-1H-indole-2,3-dione-3-(O-methyloxime), M.p. 167-170 °C.  
 5,6-dichloro-1-methyl-1H-indole-2,3-dione-3-(O-methyloxime), M.p. 202-204 °C.  
 4,5-dichloro-1-methyl-1H-indole-2,3-dione-3-(O-

methyloxime), M.p. 180-183 °C.  
 5,7-dinitro-1-benzyl-1H-indole-2,3-dione-3-(O-methyloxime), M.p. 181-185 °C.  
 4,6-ditrifluoromethyl-1-methyl-1H-indole-2,3-dione-3-(O-methyloxime), M.p. 99-100 °C.  
 5-nitro-7-trifluoromethyl-1-methyl-1H-indole-2,3-dione-3-(O-methyloxime), M.p. 160-161 °C.  
 5-nitro-7-trifluoromethyl-1H-indole-2,3-dione-3-(O-methyloxime), M.p. 225-228 °C.  
 5,7-dinitro-6-methoxy-1-methyl-1H-indole-2,3-dione-3-(O-methyloxime), M.p. 145-148 °C.  
 5,7-dinitro-1-(O-ethylcarboxymethyl)-1H-indole-2,3-dione-3-(O-methyloxime), M.p. 115-117 °C.  
 5-nitro-1-methyl-1H-benz[g]indole-2,3-dione-3-(O-methyloxime), M.p. 255-258 °C.  
 5-bromo-1-(ethoxycarbonylmethyl)-1H-indole-2,3-dione-3-(O-methyloxime), M.p. 201-204 °C.  
 5,7-dibromo-1-(ethoxycarbonylmethyl)-1H-indole-2,3-dione-3-(O-methyloxime), M.p. 137-138 °C.  
 5-methyl-1-(methoxycarbonylmethyl)-1H-indole-2,3-dione-3-(O-methyloxime), M.p. 127-131 °C.  
 5-nitro-1-methyl-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione-3-(O-methyloxime), M.p. 220-224 °C.  
 Substitution of O-methyl-hydroxylamine hydrochloride in the process by hydroxylamine hydrochloride, afforded the following oximes.  
 1H-benz[g]indole-2,3-dione-3-oxime, M.p. 248-250 °C.  
 5,7-dinitro-1-methyl-1H-indole-2,3-dione-3-oxime, M.p. 244 °C (decomp.).  
 5,7-dibromo-1H-indole-2,3-dione-3-oxime, M.p. 240-242 °C.  
 5-bromo-1-methyl-1H-indole-2,3-dione-3-oxime, M.p. 213-215 °C.  
 5,7-dinitro-1H-indole-2,3-dione-3-oxime, M.p. 240-242 °C.  
 5-bromo-7-nitro-1H-indole-2,3-dione-3-oxime, M.p. 254-256 °C.  
 5-bromo-1H-indole-2,3-dione-3-oxime, M.p. 250-251 °C.  
 5-nitro-1H-indole-2,3-dione-3-oxime, M.p. 243-245 °C.  
 5-methyl-1H-indole-2,3-dione-3-oxime, M.p. 203-206 °C.  
 1H-indole-2,3-dione-3-oxime, M.p. 234-236 °C.  
 1-methyl-6,7,8,9-tetrahydro-1H-benz[g]indole-2,3-dione-3-oxime, M.p. 230-232 °C.  
 5,6-dichloro-1-methyl-1H-indole-2,3-dione-3-oxime, M.p. 232-236 °C.  
 4-phenyl-7-methoxy-1H-indole-2,3-dione-3-oxime, M.p. 201-204 °C.  
 4,5-dichloro-1H-indole-2,3-dione-3-oxime, M.p. 245-247 °C.  
 1-phenyl-1H-indole-2,3-dione-3-oxime, M.p. 166-170 °C.  
 4,5-dichloro-1-methyl-1H-indole-2,3-dione-3-oxime, M.p. 140-142 °C.

5-nitro-1H-benz[g]indole-2,3-dione-3-oxime, M.p. 197-199 °C.

5-nitro-7-trifluoromethyl-1-methyl-1H-indole-2,3-dione-3-oxime, M.p. 204-205 °C.

5-nitro-7-trifluoromethyl-1H-indole-2,3-dione-3-oxime, M.p. 230-232 °C.

5-nitro-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione-3-oxime, M.p. 205-210 °C.

5-fluoro-7-nitro-1H-indole-2,3-dione-3-oxime, M.p. 260-262 °C.

5,7-dinitro-1-(ethoxycarbonylmethyl)-1H-indole-2,3-dione-3-oxime, M.p. 217-220 °C.

1-(ethoxycarbonylmethyl)-1H-indole-2,3-dione-3-oxime, M.p. 183-185 °C.

5-bromo-1-(ethoxycarbonylmethyl)-1H-indole-2,3-dione-3-oxime, M.p. 178-181 °C.

5,7-dinitro-1H-indole-2,3-dione-3-oxime, M.p. 195-197 °C.

Substitution of hydroxylamine hydrochloride in the process by O-benzylhydroxylamine, afforded the following compounds.

5,7-dinitro-1H-indole-2,3-dione-3-(O-benzylloxime), M.p. 197-199 °C.

5,7-dinitro-1H-1-benzyl-indole-2,3-dione-3-(O-benzylloxime), M.p. 148-150 °C.

5,7-dinitro-1-methyl-1H-indole-2,3-dione-3-(O-benzylloxime), M.p. 120-125 °C.

5,7-dinitro-1-(ethoxycarbonylmethyl)-1H-indole-2,3-dione-3-(O-benzylloxime), M.p. 100-102 °C.

5-nitro-1-(ethoxycarbonylmethyl)-1H-indole-2,3-dione-3-(O-benzylloxime), M.p. 185-187 °C.

The following compounds were prepared according to literature procedures: 1-methoxy-1H-indole-2,3-dione-3-oxime, M.p. 166-168 °C.<sup>11</sup>

1-acetyl-5-bromo-1H-indole-2,3-dione, M.p. 133-135 °C.

1-hydroxy-1H-indole-2,3-dione-3-oxime, M.p. 217-221 °C.<sup>11</sup>

### Example 3

a) 1-carboxymethyl-1H-indole-2,3-dione.

8.39 g (36 mmol) 1-(ethoxycarbonylmethyl)-1H-indole-2,3-dione and 4N NaOH (10 ml, 40 mmol) were dissolved in 30 ml H<sub>2</sub>O and 10 ml absolute ethanol and the mixture was heated at reflux for 30 minutes. The reaction mixture was cooled and added excess hydrochloric acid. The precipitate was isolated. Yield of title compound is 6.2 g.

b) 1-chlorocarbonylmethyl-1H-indole-2,3-dione.

1 g of the product prepared under a) was suspended in toluene (10 ml) and SOCl<sub>2</sub> (1.0 ml, 13.78 mmol) was added. The mixture was stirred at RT for 2 hours and additionally at

70 °C for 30 minutes and thereafter at reflux for 1 hour. The reaction mixture was stirred at RT overnight whereafter the precipitated yellow crystals were isolated and washed with toluene. Yield of title compound was 1.3 g including solvent content.

c) 1-aminocarbonylmethyl-1H-indole-2,3-dione.

The product prepared under b) was dissolved in dry THF (50 ml) and to the solution was added liquid NH<sub>3</sub>. The resulting mixture was stirred overnight at RT. The precipitated orange crystals were isolated and were washed with water. Yield of title compound was 0.46 g.

d) 1-cyanomethyl-1H-indole-2,3-dione.

Triphenylphosphine (0.75 g, 2.84 mmol) was dissolved in methylenechloride and to the solution was added dropwise to Br<sub>2</sub> (0.15 ml, 2.84 mmol) in methylenechloride (20 ml). To this mixture the product prepared under c) was added, and thereafter triethylamine (0.8 ml, 5.68 mmol) was added dropwise. The mixture was stirred for 30 minutes. The reaction mixture was evaporated in vacuo and the residue was taken up in ether. The precipitate from this mixture was filtered off and the ether solution was washed with water and dried (MgSO<sub>4</sub>). The ether solution was evaporated in vacuo and the residue was washed with isopropanol. Yield of title compound was 0.11 g. M.p. 125-128 °C.

e) 1-(acetamideoxime-2-yl)-1H-indole-2,3-dione-3-oxime.

The product prepared under d) (90 mg, 0.48 mmol), hydroxylamine hydrochloride (70 mg, 1.06 mmol), potassium carbonate (150 mg, 1.06 mmol) and methanol (10 ml) were mixed and the mixture was stirred at RT overnight. The reaction mixture was evaporated in vacuo. The residue was washed with water containing small amounts of acetic acid. Yield of title compound was 70 mg. M.p. 227-229 °C.

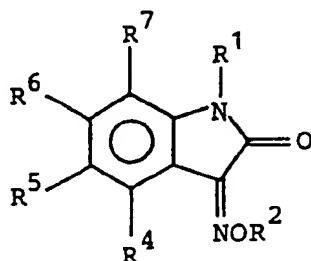
It is thus seen that the present invention provides a new and convenient process for the production of indole-2,3-dione-3-oxime compounds, certain novel indole-2,3-dione-3-oxime compounds which are useful as excitatory amino acid antagonists, pharmaceutical-compositions useful as excitatory amino acid antagonists comprising certain indole-2,3-dione-3-oxime compounds, and a method of antagonizing the biological effects of excitatory amino acids in a subject in need thereof comprising the step of administering certain indole-2,3-dione-3-oxime compounds or a pharmaceutical composition comprising the same together with a pharmaceutically-acceptable diluent or carrier, all having the foregoing characteristics and advantages.

<sup>11</sup>A. Reiszert, Ber. vol. 41, 3921.

It is to be understood that the invention is not to be limited to the exact details of operation, or to the exact methods, procedures, or embodiments shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the full scope of the appended claims.

### Claims

1. The use of an indole-2,3-dione-3-oxime compound having the formula



wherein

R<sup>1</sup> is hydrogen, C<sub>1-6</sub>-alkyl which may be branched, C<sub>3-7</sub>-cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C<sub>1-6</sub>-alkoxy, CH<sub>2</sub>CO<sub>2</sub>R' wherein R' is hydrogen or C<sub>1-6</sub>-alkyl which may be branched, CH<sub>2</sub>CN, CH<sub>2</sub>CONR<sup>IV</sup>R<sup>V</sup> wherein R<sup>IV</sup> and R<sup>V</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, or CH<sub>2</sub>C(=NOH)NH<sub>2</sub>;

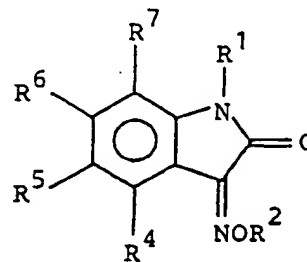
R<sup>2</sup> is hydrogen, benzyl, C<sub>1-6</sub>-alkyl which may be branched, or C<sub>3-7</sub>-cycloalkyl;

R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl which may be branched, phenyl, halogen, C<sub>1-6</sub>-alkoxy, NO<sub>2</sub>, CN, CF<sub>3</sub>, or SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl; or R<sup>6</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, and R<sup>4</sup> and R<sup>5</sup> have the meanings set forth above, for the preparation of a medicament useful in the treatment of conditions sensitive to an excitatory amino acid.

2. The use according to claim 1 wherein at least one of R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup> is an electron withdrawing substituent such as NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''', or halogen and R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R'', and R''' otherwise have the meanings set forth in claim 1.

3. The use according to claim 1 wherein R<sup>5</sup> is NO<sub>2</sub>, F, CF<sub>3</sub>, or CN.

4. A pharmaceutical composition for use in antagonizing the biological effects of an excitatory amino acid of a subject in need of such antagonization comprising an effective excitatory amino acid antagonizing amount of a compound having the formula



R<sup>1</sup> is hydrogen;

R<sup>2</sup> is hydrogen, benzyl, C<sub>1-6</sub>-alkyl which may be branched, or C<sub>3-7</sub>-cycloalkyl;

R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl which may be branched, phenyl, halogen, C<sub>1-6</sub>-alkoxy, NO<sub>2</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CF<sub>3</sub>, or R<sup>6</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, and R<sup>4</sup> and R<sup>5</sup> have the meanings set forth above, at least one of R<sup>4</sup>, R<sup>6</sup> and R<sup>7</sup> are other than hydrogen when R<sup>5</sup> is not other than H, Cl or Br;

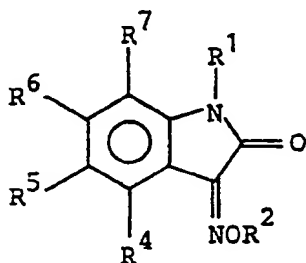
or R<sup>1</sup> is C<sub>1-6</sub>-alkyl which may be branched, C<sub>3-7</sub>-cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C<sub>1-6</sub>-alkoxy, CH<sub>2</sub>CO<sub>2</sub>R' wherein R' is hydrogen or C<sub>1-6</sub>-alkyl which may be branched, CH<sub>2</sub>CN, CH<sub>2</sub>CONR<sup>IV</sup>R<sup>V</sup> wherein R<sup>IV</sup> and R<sup>V</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, CH<sub>2</sub>C(=NOH)NH<sub>2</sub>;

R<sub>2</sub> is hydrogen, benzyl, C<sub>1-6</sub>-alkyl which may be branched, or C<sub>3-7</sub>-cycloalkyl;

R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl which may be branched, phenyl, halogen, C<sub>1-6</sub>-alkoxy, NO<sub>2</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CF<sub>3</sub>, or R<sup>6</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl.

and  $R^4$  and  $R^5$  have the meanings set forth above, at least one of  $R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  are other than hydrogen when  $R^1$  is not other than methyl, at least one of  $R^4$  and  $R^5$  are other than hydrogen when  $R^1$  is not other than phenyl which may be substituted, and at least one of  $R^4$  and  $R^5$  are other than hydrogen when  $R^5$  and  $R^7$  together form an additional benzene ring, together with at least one pharmaceutically acceptable carrier and/or diluent.

5. A compound having the formula



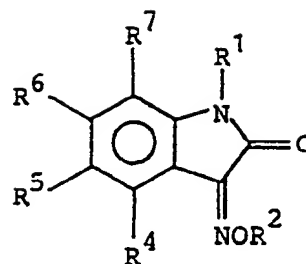
wherein  $R^1$  is  $C_{1-6}$ -alkyl which may be branched,  $C_{3-7}$ -cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy,  $C_{1-5}$ -alkoxy,  $CH_2CO_2R'$  wherein  $R'$  is hydrogen or  $C_{1-6}$ -alkyl which may be branched,  $CH_2CN$ ,  $CH_2CONR''R'''$  wherein  $R''$  and  $R'''$  independently are hydrogen or  $C_{1-5}$ -alkyl, or  $CH_2C(=NOH)NH_2$ ;

$R^2$  is hydrogen, benzyl,  $C_{1-6}$ -alkyl which may be branched, or  $C_{3-7}$ -cycloalkyl;

$R^5$  is  $NO_2$ , F,  $CF_3$ ,  $SO_2NR''R'''$  wherein  $R''$  and  $R'''$  independently are hydrogen or  $C_{1-5}$ -alkyl, or CN; and

$R^4$ ,  $R^6$ ,  $R^7$  independently are hydrogen,  $C_{1-6}$ -alkyl which may be branched, phenyl, halogen,  $C_{1-5}$ -alkoxy,  $NO_2$ , CN,  $SO_2NR''R'''$  wherein  $R''$  and  $R'''$  independently are hydrogen or  $C_{1-6}$ -alkyl, or  $CF_3$ , or  $R^6$  and  $R^7$  together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen,  $NO_2$ ,  $CF_3$ , CN,  $SO_2NR''R'''$  wherein  $R''$  and  $R'''$  independently are hydrogen or  $C_{1-6}$ -alkyl, and  $R^4$  has the meaning set forth above.

6. A compound having the formula



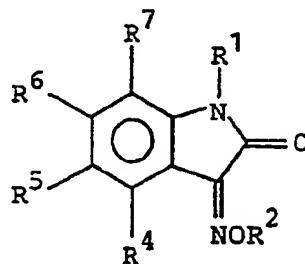
wherein  $R^1$  is  $C_{1-6}$ -alkyl which may be branched,  $C_{3-7}$ -cycloalkyl, benzyl, acyl, hydroxy,  $C_{1-6}$ -alkoxy,  $CH_2CO_2R'$  wherein  $R'$  is hydrogen or  $C_{1-6}$ -alkyl which may be branched,  $CH_2CN$ ,  $CH_2CONR''R'''$  wherein  $R''$  and  $R'''$  independently are hydrogen or  $C_{1-5}$ -alkyl, or  $CH_2C(=NOH)NH_2$ ;

$R^2$  is hydrogen, benzyl,  $C_{1-6}$ -alkyl which may be branched, or  $C_{3-7}$ -cycloalkyl;

$R^5$  is  $NO_2$ , F,  $CF_3$ ,  $SO_2NR''R'''$  wherein  $R''$  and  $R'''$  independently are hydrogen or  $C_{1-5}$ -alkyl, or CN; and

$R^4$ ,  $R^6$ ,  $R^7$  independently are hydrogen,  $C_{1-6}$ -alkyl which may be branched, phenyl, halogen,  $C_{1-6}$ -alkoxy,  $NO_2$ , CN,  $SO_2NR''R'''$  wherein  $R''$  and  $R'''$  independently are hydrogen or  $C_{1-6}$ -alkyl, or  $CF_3$ , or  $R^6$  and  $R^7$  together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen,  $NO_2$ ,  $CF_3$ , CN,  $SO_2NR''R'''$  wherein  $R''$  and  $R'''$  independently are hydrogen or  $C_{1-6}$ -alkyl, and  $R^4$  has the meaning set forth above.

7. A compound having the formula



wherein

$R^1$  is hydrogen,

$R^2$  is hydrogen, benzyl,  $C_{1-6}$ -alkyl which may be branched, or  $C_{3-7}$ -cycloalkyl;

$R^5$  is  $NO_2$ , F,  $CF_3$ ,  $SO_2NR''R'''$  wherein  $R''$  and  $R'''$  independently are hydrogen or  $C_{1-5}$ -alkyl, or CN; and

$R^4$ ,  $R^6$ ,  $R^7$  independently are hydrogen,  $C_{1-6}$ -alkyl which may be branched, phenyl, halogen,  $C_{1-6}$ -alkoxy,  $NO_2$ , CN,  $SO_2NR''R'''$  wherein

R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CF<sub>3</sub>, or R<sup>6</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, and R<sup>4</sup> has the meaning set forth above; and that R<sup>5</sup> is different from NO<sub>2</sub> and F when R<sup>1</sup>, R<sup>4</sup>, R<sup>6</sup> and R<sup>7</sup> are not other than hydrogen and R<sup>2</sup> is not other than hydrogen or benzyl; and that R<sup>5</sup> is different from NO<sub>2</sub> when R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup> and R<sup>6</sup> are not other than hydrogen and R<sup>7</sup> is not other than NO<sub>2</sub>.

8. A compound according to claim 6 or 7 wherein R<sup>4</sup> and R<sup>5</sup> independently are hydrogen, F, NO<sub>2</sub>, CN, CF<sub>3</sub>, or SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, and wherein R<sup>6</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl.

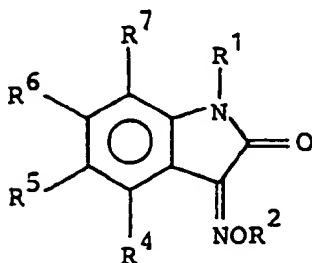
9. A compound according to claim 8 wherein the additional ring formed by R<sup>6</sup> and R<sup>7</sup> is substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN or SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl.

10. A compound of Claim 7, which is 5-nitro-1H-benz[g]indole-2,3-dione-3-oxime.

11. A compound of Claim 6, which is 5,7-dinitro-1-methyl-1H-indole-2,3-dione-3-(O-methyloxime).

12. A compound of Claim 7, which is 5-nitro-1H-6,7,8,9-tetrahydro-benz[g]indole-2,3-dione-3-oxime.

13. A method of preparing a compound having the formula



wherein R<sup>1</sup> is hydrogen, C<sub>1-6</sub>-alkyl which may be branched, C<sub>3-7</sub>-cycloalkyl, benzyl, phenyl

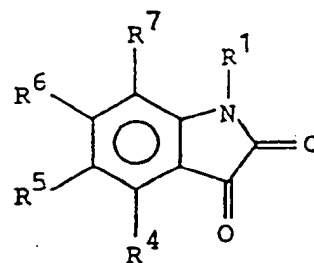
which may be substituted, acyl, hydroxy, C<sub>1-6</sub>-alkoxy, CH<sub>2</sub>CO<sub>2</sub>R' wherein R' is hydrogen or C<sub>1-6</sub>-alkyl which may be branched, CH<sub>2</sub>CN, CH<sub>2</sub>CONR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CH<sub>2</sub>C(=NOH)NH<sub>2</sub>;

R<sup>2</sup> is hydrogen, benzyl, C<sub>1-6</sub>-alkyl which may be branched, or C<sub>3-7</sub>-cycloalkyl;

R<sup>5</sup> is NO<sub>2</sub>, F, CF<sub>3</sub>, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, or CN; and

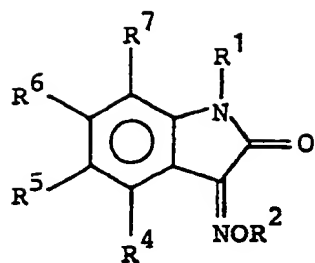
R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl which may be branched, phenyl, halogen, C<sub>1-6</sub>-alkoxy, NO<sub>2</sub>, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl,

CN, or CF<sub>3</sub>, or R<sup>5</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR''R''' wherein R'' and R''' independently are hydrogen or C<sub>1-6</sub>-alkyl, and R<sup>4</sup> has the meaning set forth above; and that R<sup>5</sup> is different from NO<sub>2</sub> and F when R<sup>1</sup>, R<sup>4</sup>, R<sup>6</sup> and R<sup>7</sup> are not other than hydrogen and R<sup>2</sup> is not other than hydrogen or benzyl; and that R<sup>5</sup> is different from NO<sub>2</sub> when R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup> and R<sup>6</sup> are not other than hydrogen and R<sup>7</sup> is not other than NO<sub>2</sub>, comprising the step of reacting a compound of the formula



wherein R<sup>1</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> have the meanings set forth above, with a compound having the formula NH<sub>2</sub>OR<sup>2</sup>, wherein R<sup>2</sup> has the meaning set forth above.

14. A method of preparing a pharmaceutical preparation comprising mixing as active ingredient an effective amount of a compound having the formula



wherein

R¹ is hydrogen, C₁-₆-alkyl which may be branched, C₃-₇-cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C₁-₅-alkoxy, CH₂CO₂R' wherein R' is hydrogen or C₁-₅-alkyl which may be branched, CH₂CN, CH₂CONR⁴R⁵ wherein R⁴ and R⁵ independently are hydrogen or C₁-₆-alkyl, or CH₂C(=NOH)NH₂;

R² is hydrogen, benzyl, C₁-₅-alkyl which may be branched, or C₃-₇-cycloalkyl;

R³, R⁴, R⁵, R⁶ independently are hydrogen, C₁-₆-alkyl which may be branched, phenyl, halogen, C₁-₅-alkoxy, NO₂, CN, SO₂NR''R''' wherein R'' and R''' independently are hydrogen or C₁-₆-alkyl, or CF₃; or R⁴ and R⁵ together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO₂, CF₃, CN, SO₂NR''R''' wherein R'' and R''' independently are hydrogen or C₁-₆-alkyl, and R⁴ and R⁵ have the meanings set forth above, with at least one pharmaceutically acceptable carrier and/or diluent.



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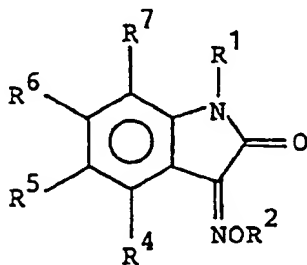
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54 Isatine derivatives, their preparation and use.

57 A method of treatment with compounds having the formula



where in

R<sup>1</sup> is hydrogen, C<sub>1-6</sub>-alkyl which may be branched, C<sub>3-7</sub>-cycloalkyl, benzyl, phenyl which may be substituted, acyl, hydroxy, C<sub>1-6</sub>-alkoxy, CH<sub>2</sub>CO<sub>2</sub>R' wherein R' is hydrogen or C<sub>1-6</sub>-alkyl which may be branched, CH<sub>2</sub>CN, CH<sub>2</sub>CONR<sup>M</sup>R<sup>V</sup> wherein R<sup>M</sup> and R<sup>V</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, or

CH<sub>2</sub>C(=NOH)NH<sub>2</sub>;

R<sup>2</sup> is hydrogen, benzyl, C<sub>1-6</sub>-alkyl which may be branched, or C<sub>3-7</sub>-cycloalkyl;

R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl which may be branched, phenyl, halogen, C<sub>1-6</sub>-alkoxy, NO<sub>2</sub>, CN, SO<sub>2</sub>NR<sup>''</sup>R<sup>'''</sup> wherein R<sup>''</sup> and R<sup>'''</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, or CF<sub>3</sub>; or R<sup>6</sup> and R<sup>7</sup> together form an additional 4 to 7 membered ring which may be aromatic or partial saturated and which may be substituted with halogen, NO<sub>2</sub>, CF<sub>3</sub>, CN, SO<sub>2</sub>NR<sup>''</sup>R<sup>'''</sup> wherein R<sup>''</sup> and R<sup>'''</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, and R<sup>4</sup> and R<sup>5</sup> have the meanings set forth above, are disclosed, as well as pharmaceutical compositions thereof. Certain of the compounds are novel.

The compounds and pharmaceutical compositions containing the compounds are useful in the treatment of central nervous system disorders and especially conditions sensitive to excitatory amino acids.

EP 0 432 648 A3



European  
Patent Office

# EUROPEAN SEARCH REPORT

Application Number

EP 90 12 3474

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 010 398 (FUJISAWA PHARMACEUTICAL CO.LTD.) * pages 1 - 3, line 16 * - - - -	1,6	C 07 D 209/40 A 61 K 31/40
A	CHEMICAL ABSTRACTS, vol. 103, no. 3, 22 July 1985 Columbus, Ohio, USA Cedere D. et al.: "Reversible inhibitors of monoamine oxidase in the indoline series" page 17; column 1; ref. no. 16405S & Khim.-Farm.Zh.1984 vol.18,no.5,pages 555-8 * abstract * - - - -	1,6	
A,D	Wissenschaftliche Zeitschrift der Ernst-Moritz-Arndt-Universität Greifswald.Mathematisch-Naturwissenschaftliche Reihe vol. XXXV, no. 4, 1986, DDR pages 39 - 44; Susanne Baehnisch et al.: "Zur Wirkung substituierter Indoline am isolierten Rattenfundusstreifen" * the whole document * - - - -	1,6	
A,D	Die Pharmazie vol. 39, no. 10, October 1984, DDR page 713 W.Fischer et al.: "Indoline und serotonerge Effekte an isolierten Organpräparaten" * the whole document * - - - -	1,6	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
A,D	Die Pharmazie vol. 37, no. 12, December 1982, DDR pages 858 - 861; W.Fischer et al.: "Antikonvulsive Wirkungen von Indolinderivaten" * the whole document * - - - - -	1,6	C 07 D 209/00
The present search report has been drawn up for all claims			
Place of search Berlin		Date of completion of search 23 July 91	Examiner KYRIAKAKOU G
<b>CATEGORY OF CITED DOCUMENTS</b> X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention  E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons  &: member of the same patent family, corresponding document			